MUCRONIN — A NEW GERMACRANOLIDE FROM *Tanacetopsis mucronata*

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Balchanolide and a new sesquiterpene lactone, mucronin, $C_{15}H_{22}O_3$ with mp 132°C, $[\alpha]_D^{20}$ + 23.7° (c 0.18; chloroform) have been isolated from the epigeal part of *Tanacetopsis mucronata*. It has been established that mucronin has the structure of 6βH,8βH,11αH-germacra-1(10),4(5)-dien-6,12-olide).

Continuing a study of the sesquiterpenoids of the epigeal part of the plant *Tanacetopsis mucronata* (Regel et Schmalh.) S. Kovalevsk. [1], collected in the period of full flowering in the Hissar range, TadzhSSR, in addition to the deacetyllaurenobiolide, deacetyldehydrolaurenobiolide, tavulin, tanachin, and mucrin [2], we have isolated another two lactones.

The first lactone had the composition $C_{15}H_{10}O_3$ (II), M^+ 250, mp 152-154°C (hexane—ethyl acetate), $[\alpha]_D^{20}$ + 102° (c 0.18; $CHCl_3$). Its IR spectrum (ν_{max}, KBr) showed absorption bands at (cm^{-1}) 3550 (OH), 1760 (γ-lactone carbonyl), and 1680 (C═C), and it gave a monoacetate with the composition $C_{17}H_{24}O_4$ (II), mp 122°C (hexane—ethyl acetate). The lactone (II) was identified as balchanolide [3, 4].

The second lactone, with the composition $C_{15}H_{22}O_3$ (III), mp 132°C (hexane—ethyl acetate), $[\alpha]_D^{20}$ + 23.7° (c 0.18; $CHCl_3$), proved to be new and we have called it mucronin. The IR spectrum of (III) showed absorption bands at (cm^{-1}) 1765 (γ-lactone carbonyl) and 1680 (C═C). In addition, there was the absorption of a hydroxy group (3530 cm^{-1}), as was confirmed by the mass spectrum, which contained the peaks of the molecular ion with m/z 250 (M^+, 10%) and of an ion with m/z 232 (M^+ — 18, 13%), showing the presence of a hydroxy group.

The PMR spectrum of (II) taken in C_5D_5N showed the signals of the protons of a secondary methyl group in the form of a three-proton doublet at 1.50 ppm, J = 7.5 Hz, and of two methyl groups at a double bond (1.26 ppm, s, and 1.36 ppm, s). A one-proton doublet at 6.05 ppm with J = 5 Hz related to the hydroxylic proton. In the 4.35-4.85 ppm region there were the signals of two olefinic, of one lactonic, and of one gem-hydroxylic proton.

The facts given and the composition permitted lactone (III) to be regarded as a germacranolide, and this was also confirmed by the fact that the mass spectra of mucronin and of balchanolide contain the same sets of ions. When mucronin was acetylated with acetic anhydride in pyridine, a monoacetyl derivative was formed with the composition $C_{17}H_{24}O_4$ (IV), M^+ 292, mp 158-160°C (hexane—ethyl acetate). The PMR spectra of (IV) taken in C_5D_5N (see Table 1) showed the signals of a secondary methyl group in the form of a doublet at 1.13 ppm, 3 H, J = 7.7 Hz, while in the spectrum of (IV) recorded in $CDCl_3$ the signal of an olefinic proton appeared clearly in the form of a multiplet at 4.8 ppm with $W_{1/2}$ = 20 Hz. The $W_{1/2}$ value of the signal of this olefinic proton is obviously due to vicinal and remote (aryl) interactions with CH_3 protons. Consequently, one double bond is located between C_1 and C_{10}. It can be seen from Table 1 that the CS of the signal of the 11-CH_3 group of (IV) is 1.17 ppm.

The PMR spectrum of mucronin (III) in C_5D_5N showed a one-proton quintet with its center at 3.07 ppm and equal values of the SSCCs (^3J) between the components of 7.5 Hz and a ratio of the intensities of 1:3:4:3:1, showing that there were four protons adjacent to it. The quintet at 3.07 ppm obviously belongs to the H-11 proton, which interacts with three protons of the secondary CH_3 group and the H-7 proton with a ^3J value of 7.5 Hz. This hypothesis was completely confirmed by double resonance in the INDOR regime. The INDOR spectra on the extreme nondegenerate lines of the quintet at 3.07 ppm showed that the H-11 proton interacted with the protons of the CH_3—CH—doublet with its center at 1.50 ppm and with a proton giving a signal in the 2.40-2.15 ppm region (H-7). The value of the $^3J_{H-7,H-11}$ SSCC, 7.5 Hz,

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TABLE 1. Chemical shifts of the Protons of Balchanolide and Mucronin and Their Derivatives (δ, ppm, 0 — HMDS)

Proton	I		II			III	IV		
	C_5D_5N	$CDCl_3$	C_5D_5N	$CDCl_3$	C_6D_6	C_5D_5N	C_5D_5N	$CDCl_3$	C_6D_6
H-1	4,5—4,8	4,5—5,0	4,43—4,8	4,5—4,93	4,35 m	4,7—4,85	4,35—4,8	4,8 m	4,42 t
H-5	4,5—4,8	4,5—9,0	4,43—4,8	4,5—4,93	4,17 $J = 10$	4,7—4,85	4,35—4,8	4,2—4,55	4,11 d $J = 10$
H-6	4,5—4,8	4,5—5,0	4,43—4,8	4,5—4,93	4,07 t $J_1 = J_2 = 10$	4,45 t $J_1 = J_2 = 10$	4,35—4,8	4,2—4,55	4,00 d $J_1 = J_2 = 10$
H-8	3,98 sex ${}^3J_1 = {}^3J_2 = 10;$ ${}^3J_3 = 2$	3,85 ${}^3J_1 = {}^3J_2 = 10;$ ${}^3J_3 = 2$	5,13 ${}^3J_1 = {}^3J_2 = 10;$ ${}^3J_3 = 2$	5,04 ${}^3J_1 = {}^3J_2 = 10;$ ${}^3J_3 = 2$	4,75 ${}^3J_1 = {}^3J_2 = 10;$ ${}^3J_3 = 2$	4,55 ${}^3J_1 = {}^3J_2 =$ $= 10;$ ${}^3J_3 = 2$	5,43 t ${}^3J_1 = {}^3J_2 = 10$	5,24 t ${}^3J_1 = {}^3J_2 = 10$ (5,33 t)	5,11 t ${}^3J_1 = {}^3J_2 = 10$ (5,20 t)
4-CH_3	1,46 s	1,61 s	1,44 s	1,62 s	1,56 s	1,36 s	1,61 s	1,67 s (1,73 s)	1,49 s (1,56 s)
10-CH_3	1,26 s	1,38 s	1,36 s	1,45 s	1,25 s	1,26 s	1,29 s	1,42 s	1,03 s (1,14 s)
11-CH_3	1,62 d $J = 7,5$	1,38 d $J = 7,5$	1,36 d $J = 7,5$	1,32 d $J = 7,5$	1,29 d $J = 7,5$	1,50 d $J = 7,5$	1,13 d $J = 7,5$	1,17 d (1,21 d) $J = 7,5$	0,90 d (1,00 d) $J = 7,5$
OH	6,30 d $J = 5$	—	—	—	—	6,05 d $J = 5$	—	—	—
OAc	—	—	1,93 s	2,03 s	—		1,89 s	1,95 s (2,00 s)	1,49 s (1,62 s)

Note: s — singlet; d — doublet; t — triplet; sex — sextet. The chemical shifts in parentheses are given relative to TMS as internal standard.

showed that the H-11 proton had the α-pseudoequatorial orientation [5]. This was also confirmed by a study of the CS of the signal of the protons of the secondary methyl group of the acetate (IV) in $CDCl_3$ and C_6D_6. It has been shown [5] that the difference in the CSs of the signals of the protons of the group in $CDCl_3$ and C_6D_6 changes substantially according to the orientation of the methyl group. Thus, in the case of (IV) the table shows a difference of the CSs of the 11-CH_3—CH group, $\Delta\delta(CDCl_3 - C_6D_6)$ of +0.21 ppm, which shows the β-pseudoaxial orientation of the methyl group and confirms, correspondingly, the α-pseudoequatorial orientation of the H-11 proton.

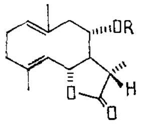
In the PMR spectrum of (IV) in C_6D_6 (see Table 1), the signal of the lactone proton was observed in the form of a triplet at 4.00 ppm with ^3J = 10 Hz, and the signal of the second olefinic proton at 4.11 ppm, in the form of a doublet (J = 10 Hz). Consequently, the H_5 and H_7 protons in vicinal positions with respect to the lactone proton had the trans-diaxial orientation and the second double bond was located between C_4 and C_5.

In order to establish the position of the OH group and that of the lactone ring in (III), we again used INDOR experiments. The signal of the H-6 lactone proton in the spectrum of (III) appeared in the form of a triplet with ^3J = 10 Hz and its center at 4.45 ppm, and this value of the SSCC showed the trans-diaxial orientation of the H-6 and H-7 protons. An INDOR signal on an extreme line of the H-6 triplet showed that this proton interacts with one of the olefinic protons giving a signal at 4.7 ppm and with the H-7 proton with a signal in the 2.40-2.15 ppm region and that the lactone ring is located at C_6—C_7.

The hydroxy group could be present at C_8 or C_3. The signal of the gem-hydroxylic proton in the spectrum of (III) appeared in the form of a sextet with its center at 4.55 ppm and $^3J_1 = {}^3J_2$ = 10 Hz and $^3J_3$ = 2 Hz. The INDOR signals on the extreme lines of this sextet showed that this proton interacted with the signals in the 2.40-2.15 ppm region and with a doublet having broadened components at 2.75 ppm. As we had already established, the signal in the 2.40-2.15 ppm region related to H-7 and, therefore, the H-7 proton also interacted with the H-8 proton geminal to the OH group located at C_8.

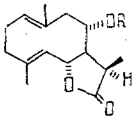
A comparative analysis of the PMR results showed that the structure of substance (II) differed from that of balchanolide only by the orientation of the methyl group at C_{11}. In view of this, we determined the nature of the orientation of the methyl group a C_{14} in balchanolide [$\Delta\delta = (CDCl_3 - C_6D_6) = +0.03$] and confirmed its pseudoequatorial orientation [5]. It must be mentioned that balchanolide acetate is a dihydro product of tulipinolide [6] and the acetate of our substance (IV) is its epimer at C_{11} [7].

Thus, mucronin has the structure and configuration of 6βH,8β,11α-germacra-1(10),4-dien-6,12-olide.



I. R = H

II. R = $COCH_3$



III. R = H

IV. R = $COCH_3$

EXPERIMENTAL

IR spectra were taken on a UR-20 spectrophotometer (KBr), mass spectra on a MKh 1303, and PMR spectra on a JNM-4H-100 MHz instrument. The INDOR spectra of mucronin were obtained on a Varian XL-100 spectrometer in C_5D_5N. The chemical shifts are given in the δ scale relative to the signal of HMDS taken as 0.

Thin-layer chromatography (TLC) was performed on Silufol UV-254 plates, the spots being revealed with sulfuric acid containing 1% of vanillin. The ethyl acetate—hexane (3:2) solvent system was used.

Isolation of the Lactones. The epigeal part of the plant (50 kg) was extracted with chloroform (1:5) five times for 24 h each time. The solvent was distilled off in vacuum. The resin was treated with 60% ethanol. The lactones were extracted from the ethanolic solution with chloroform. The resin (1 kg) was chromatographed on KSK silica gel in a ratio of 1:4. Elution was performed with benzene and benzene—ethyl acetate (98:2) with a subsequent increase in the proportion of ethyl acetate. The benzene eluates were combined and chromatographed on silica gel (1:10) with elution by the hexane—ethyl acetate (9:1) and (4:1) systems. The fractions eluted by hexane—ethyl lacetate (4:1) were combined and were rechromatographed on silica gel (1:20). Elution was performed with hexane—methyl ethyl ketone

(9:1), the volume of the eluates being 400 ml. Fractions 1-10 yielded deacetyllaurenobiolide and deacetyldihydrolaurenobiolide. Fractions 36-41 yielded balchanolide. Fractions 11-35 were combined and rechromatographed on a column of silica gel (1:40) with elution by hexane–methyl ethyl ketone (9:1) (800 ml portions). Fractions 54-48 yielded mucronin.

Acetylation of Balchanolide. With stirring, 1.5 ml of acetic anhydride was added to a solution of 80 mg of balchanolide in 1.5 ml of pyridine. The reaction was carried out at room temperature for 2 h. After the usual working up, 50 mg of balchanolide monoacetate was obtained with mp 122°C (hexane–ethyl acetate) R_f 0.82 (R_f of the initial substance 0.60).

Acetylation of Mucronin. The reaction was performed similarly to the preceding method. From 60 mg of mucronin (R_f 0.62) was obtained 40 mg of its monoacetate (R_f 0.83) with mp 158-160°C (hexane–ethyl acetate).

CONCLUSION

Balchanolide and a new sesquiterpene lactone mucromin have been isolated from the epigeal part of *Tanacetopsis mucronata*. It has been established that mucronin is 6βH,8βH,11αH-germacra-1(10)4-dien-6,12-olide.

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